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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/654,323	HAYDEN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53 and 57-94* is/are pending in the application.

4a) Of the above claim(s) *1-49,57-79 and 92-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-53 and 80-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 1-53 and 57-94 are pending in the application.

Applicants' election with traverse of Group XVI, claims 50-53, amendment to claims 50-53, cancellation of claims 54-56, and addition of claims 80-94 in Paper No. 17, filed 07/29/02, is acknowledged.

It is noted that there is no claim 82 and there are two occurrences of claim 83 in Paper No. 17. The first occurrence of claim 83 has been re-numbered to claim 82 in accordance with 37 CFR 1.126.

Election/Restrictions

1. Applicants traverse the restriction requirement on the grounds that a search for the claims of Groups XVI-XVIII (claims 50-56) would be co-extensive and would not result in a burden on the examiner. Applicants argue the claims of Groups XVI-XVIII are interrelated, can be searched together, and should be combined into a single Group. Applicants' argument is not found persuasive. MPEP 803 sets forth two criteria for restricting between patentably distinct inventions – 1) the inventions must be independent or distinct and 2) there must be a serious burden on the examiner. Regarding the first criteria, the examiner has indicated that the inventions of Groups XVI-XVIII are distinct for the reasons provided in paragraphs 3-11 of Paper No. 14. Regarding the second criteria, the examiner has demonstrated a serious burden that would result from simultaneous search of additional Groups. MPEP 803 states, "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02". A serious burden would result from co-examination of the inventions of Groups XVI and XVII as these two inventions have separate classification - the invention of Group XVI is classified in class 435/6, while the invention of Group XVII is classified in class 707/1. A serious burden would result from co-examination of the inventions of Groups XVI and XVIII as a search for each Group would require independent considerations which would require the

examiner to focus on different features that would entail differently structured word searches for both patent and non-patent literature searches. For example, a search of Group XVIII would require the examiner to additionally search for therapies for modulating ABC1 activity or expression and methods of selection thereof that is not required for the invention of Group XVI. Therefore, because the inventions of Groups XVI-XVIII are distinct and would result in a burdensome search on the examiner, restriction for examination purposes is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-49, 57-79, and 92-94 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

1. It is noted that an Information Disclosure Statement (Form PTO-1449) has been filed with the instant application (see Paper No. 4, filed 12/04/00). However, references cited as "GenBank Accession No." fail to comply with the requirements for an IDS. See 37 CFR 1.98 and MPEP § 609 regarding content of an IDS. References cited as GenBank Accession Numbers should include an author (if available) and a publication date. Upon submission of an IDS in proper form, the examiner will consider the references and return Form PTO-1449 in a subsequent communication.

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Methods of Determining Disease Risk Based on ABC1 Polymorphisms". See MPEP § 606.01.

3. It is noted that the first paragraph of the specification improperly claims benefit of domestic priority to provisional application 60/213,958 under 35 USC 120 as a continuation-in-part application. Provisional applications are entitled to benefit of an earlier priority date under 35 USC 119(e) and not as

continuation-in-part applications under 35 USC 120. It is suggested that applicants amend the specification accordingly. See MPEP 201.04(b) regarding provisional applications.

Claim Objections

4. The first occurrence of claim 83 is objected to as not being consecutively numbered after claim 81. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claim 83 been renumbered to claim 82.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 51, 53, and 82-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 51 and 53 are unclear as to where the recited steps should be incorporated into the methods of claims 50 and 52. For example, should the additional steps occur at the end of the methods of claims 50 and 52 or at some other occurrence? It is suggested that applicants clarify the meaning of the claims.

7. Claims 82-84 and 88-90 recites the limitations "2 said polymorphisms" in claims 82 and 88, "3 said polymorphisms" in claims 83 and 89, and "5 said polymorphisms" in claims 84 and 90. There is insufficient antecedent basis for these limitations in the claims.

8. Claim 85 is confusing in the recitation of "subject, or set of subjects" as it is unclear as to whether the "subject, or set of subjects" refers to the first subject(s) or second subject(s). It is suggested that applicants clarify the meaning of the claim.

9. Claims 86 (claim 87 dependent therefrom) and 88-90 are confusing in the recitation of "at least one polymorphism that indicates the propensity for developing said disease" in claim 86 and "said polymorphisms is indicative of a propensity for developing said disease". Claim 52 is a method for determining whether a polymorphism correlates with disease. Polymorphisms that are tested may or may not be correlated with the recited diseases and therefore, may or may not be indicative of a propensity for developing the recited diseases. It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 50, 51, and 80-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 50, 51, and 80-84 are drawn to a method for determining a propensity for developing a disease or condition by determining the presence or absence of at least one, two, three, or five ABC1 polymorphism(s) in the nucleic acid sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 polypeptide, wherein the presence of a polymorphism is indicative of a propensity for developing said disease condition. The specification teaches only 12 polymorphisms in the amino acid sequence of human ABC1 that correlate with defective cholesterol efflux, i.e., the polymorphisms as shown in Figure 11. Moreover, the specification fails to

describe any other ABC1 polymorphisms by any identifying characteristics or properties other than the functionality of being a polymorphism that is indicative of a propensity or risk for developing a disease or condition. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

11. Claims 50-53 and 80-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a propensity or risk for having a lower than normal HDL level by determining the presence or absence of any of the mutations as set forth in Figure 11 in a human subject and a method for determining whether the presence of an ABC1 polymorphism in a subject is indicative of a risk for a disease selected from a lower than normal HDL level, a higher than normal triglyceride level, and a cardiovascular disease by determining a difference in the occurrence or severity of a disease in a first statistically relevant set of subjects relative to a statistically relevant set of second subjects, identifying an ABC1 polymorphism, and correlating the presence of an ABC1 polymorphism with the occurrence or severity of said disease, thereby identifying an ABC1 polymorphism that is indicative of risk, does not reasonably provide enablement for a method for determining a propensity or risk for developing a lower than normal HDL level, a higher than normal triglyceride level, and *any* cardiovascular disease by determining the presence or absence of *any* ABC1 polymorphism(s) from any source in the nucleic acid sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 polypeptide, wherein the presence of a polymorphism is indicative of a propensity or risk. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Undue experimentation would be required to make and/or use the claimed invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 50-53 and 80-91 are so broad as to encompass a method for determining a propensity or risk for developing a disease or condition by determining the presence or absence of *any* ABC1 polymorphism(s) as described above. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of ABC1 polymorphisms in the nucleic acid sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 polypeptide that are indicative of a propensity or risk for developing the recited diseases and additionally the large number of cardiovascular diseases that can be correlated to ABC1 polymorphism(s) as broadly encompassed by the claims. The specification discloses a human genomic DNA sequence having 183,999 nucleotides encoding a human ABC1 polypeptide having 2,261 amino acids. Mutation at *any* of these positions will potentially result in a propensity or risk for developing a lower than normal HDL level, a higher than normal triglyceride level, and a cardiovascular disease. The specification provides no guidance as to which of the seemingly infinite number of polymorphisms are likely to directly or indirectly alter the activity of an ABC1 promoter. While the specification discloses specific ABC1 polymorphisms (see for example Figure 11), the claims *are not limited* to one or more of the disclosed polymorphisms and the specification has not provided guidance as to which of the seemingly infinite number of polymorphisms encompassed by the claims, including nucleotide/amino acid substitutions, deletions, and/or insertions that are likely to correlate with the recited disease states. The ability to predict a specific disease state based on a polymorphic nucleic acid/polypeptide is dependent upon the correlation of an isolated polymorphism to the disease. In turn, the ability to correlate a polymorphism to a specific disease state is dependent upon the relevant correlating data. The ability to predict a propensity or risk for developing a specific phenotype is highly unpredictable and must be empirically determined in a *statistically relevant set of subjects*. A polymorphism identified in a single subject that is not present in a single second subject is not sufficient to correlate a polymorphism with a

disease state. The specification provides no guidance as to the predictability of *any* polymorphism of an ABC1 promoter or nucleic acid or amino acid sequence resulting in a propensity or risk for developing a lower than normal HDL level, a higher than normal triglyceride level, and *any* cardiovascular disease. Therefore, in order to practice the claimed invention, a skilled artisan must isolate *all* polymorphisms in an ABC1 gene or amino acid sequence from *any* source of an ABC1 promoter or nucleic acid sequence or amino acid sequence and correlate those polymorphisms to a propensity or risk for developing a lower than normal HDL level, a higher than normal triglyceride level, and *any* cardiovascular disease. Furthermore, the state of the prior art suggests that a level of unpredictability exists in genotyping disease risk as Niccoli et al. (*Int J Epidemiol* Suppl 1:S41-7, October 30, 2001) teach a "a number of studies on genetic markers [of coronary disease risk factors], on new risk factors and the interaction between genetic markers and environment have failed to withstand the rigour of population-based studies" (page S45). Therefore, undue experimentation would be required for a skilled artisan to screen for *all* ABC1 polymorphisms followed by correlating those identified with a lower than normal HDL level, a higher than normal triglyceride level, and *any* cardiovascular disease.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for determining a propensity or risk for developing a disease or condition by determining the presence or absence of *any* ABC1 polymorphism(s) as described above. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 50, 52, 80-82, 85-88, and 91 are rejected under 35 U.S.C. 102(b) as being anticipated by Rust et al. (IDS reference cited on page 2 of Paper No. 4; *Nat Genet* 22:352-355; hereafter referred to as "Rust"). Claim 50 is drawn to a method for determining a propensity for developing a disease or condition selected from a lower than normal HDL level, a higher than normal triglyceride level, and a cardiovascular disease by determining the presence or absence of at least one ABC1 polymorphism in the nucleic acid sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 polypeptide, wherein the presence of a polymorphism is indicative of a propensity for developing said disease or condition. Claims 80-82 limit the polymorphism of the method of claim 50. Claim 52 is drawn to a method for determining whether the presence of an ABC1 polymorphism in a subject is indicative of a risk for a disease or condition selected from a lower than normal HDL level, a higher than normal triglyceride level, and a cardiovascular disease by identifying at least one ABC1 polymorphism in the nucleic acid sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 polypeptide and correlating the presence of said ABC1 polymorphism with the occurrence or severity of said disease or condition. Claim 85 limits the subject of claim 52. Claims 86-88 limit the polymorphism of the method of claim 52. Claim 91 adds a step of assembling a record of polymorphisms.

Rust teaches two polymorphisms in an ABC1 amino acid sequence - a single base pair deletion at position 575 and an insertion of 38 amino acids at position 468 as compared with the published wild-type ABC1 sequence (Figure 4, page 354) – identified in subjects having Tangier Disease (TD). Rust teaches TD is characterized by lower HDL cholesterol levels and frequent premature coronary artery disease. This anticipates claims 50, 52, 80-82, 85-88, and 91 as written.

13. Claims 50-53 and 80-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Bodzioch et al. (IDS reference cited on page 1 of Paper No. 4; *Nat Genet* 22:347-351; hereafter referred to as

"Bodzioch"). Claim 50 is drawn to a method for determining a propensity for developing a disease or condition as described above. Claims 51 and 80-84 limit the polymorphism of the method of claim 50. Claim 52 is drawn to a method for determining whether the presence of an ABC1 polymorphism in a subject is indicative of a risk for a disease or condition as described above. Claim 85 limits the subject of claim 52. Claims 86-90 limit the polymorphism of the method of claim 52. Claim 91 adds a step of assembling a record of polymorphisms.

Bodzioch teaches genetic analysis of ABC1 sequences from subjects with TD led to the identification of several mutations. Homozygous TD pedigree 1 subjects exhibited a single base pair deletion at nucleotide 1764 (codon 548) and non-TD heterozygous subjects presented a decreased HDL cholesterol plasma level (page 348). TD pedigree 2 subjects exhibited a genomic deletion resulting in a presumed non-functional protein that lacks the 427 C-terminal amino acids (page 348). Homozygous TD pedigree 3 subjects exhibited an A2744G (N875S) mutation and non-TD heterozygous subjects presented a decreased HDL cholesterol plasma level (page 349). TD pedigree 4 and 5 were compound heterozygotes all having a C2750T (A877V) mutation with additional mutations resulting either in TD or lower HDL cholesterol levels (page 349). Bodzioch teaches sequence analysis of ABC1 in healthy volunteers did not reveal any of the disclosed abnormalities of TD pedigrees 1-5 (page 349). This anticipates claims 50-53 and 80-91 as written.

Conclusion

14. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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